Citation:

Virtanen JK, Mozaffarian D, Chiuve SE, Rimm EB. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr.* 2008 Dec;88(6):1618-25.

PubMed ID: 19064523

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To study associations of fish and n-3 fatty acid consumption with risk of total major chronic disease (cardiovascular disease, cancer and death) and to determine whether a high n-6 intake modifies the associations.

Inclusion Criteria:

- Participants from the Health Professionals Follow-up Study, a prospective cohort study of US male dentists, pharmacists, veterinarians, optometrists, osteopathic physicians, and podiatrists aged 40 - 75 years and free of major chronic disease at baseline in 1986

Exclusion Criteria:

- Men with baseline prevalent myocardial infarction, angina or other heart disease (e.g. aortic stenosis and heart rhythm disturbances), stroke or cancer
- Men with >70 items missing on the 131-item food frequency questionnaire
- Men with reported energy intake of <800 or >4200 kcal/day

Description of Study Protocol:

Recruitment

Participants from the Health Professionals Follow-up Study.

Design: Prospective cohort study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Cox proportional hazards models with time-varying covariates were used to evaluate risk
- Each eligible participant contributed person-time until the first diagnosis of CVD, cancer, or death or until January 31, 2004
- Fish intake was assessed in categories of <1 serving per month, 1 - 3 servings per month, 1 serving per week, 2 - 4 servings per week, and >5 servings per week
- Data from multiple food frequency questionnaires over time were used to compute cumulative averages of dietary intake
- Multivariate models were evaluated adjusted for CVD risk factors, lifestyle habits, and other dietary habits, including age, BMI, smoking, physical activity, diabetes, hypertension or hypercholesterolemia, first-degree family history of myocardial infarction before age 60 years, first-degree family history of colon cancer, aspirin use, alcohol intake, multivitamin use, and intakes of fiber, *trans* fatty acids, saturated fatty acids, α-linolenic acid, n-6 fatty acids, glycemic load, red meat and total calories
- Tests of linear trend in 5 categories were conducted by assigning the median values for each category of consumption and treating this as a continuous variable
- Correlations were evaluated by using Pearson correlation

Data Collection Summary:

Timing of Measurements

- Baseline measurements taken in 1986
- Lifestyle and other risk factors were assessed every 2 years
- Diet was assessed every 4 years (1986, 1990, 1994, 1998 and 2002)
- Participants were followed for 18 years

Dependent Variables

- Risk of major chronic disease defined as the sum of incident total CVD, total cancer or other nontraumatic death
- Deaths ascertained from relatives, postal authorities, or the National Death Index
- Cause of death was classified according to medical records, death certificates, and autopsy findings

Independent Variables

- Fish consumption based on 131-item food frequency questionnaire
- Participants were asked about consumption of the following amounts of 4 different seafood items: canned tuna fish, dark meat fish (such as mackerel, salmon, sardines, bluefish and swordfish), other fish (not specified), and shrimp, lobster or scallops as a main dish
- Intake of the marine fatty acids EPA and DHA was estimated from the consumption of all seafood
- Use of fish oil supplements was first assessed in 1988 and then every 2 years thereafter

Control Variables

- Age
- BMI
- Smoking
- Physical activity

- Diabetes, hypertension or hypercholesterolemia
- First-degree family history of myocardial infarction before age 60 years
- First-degree family history of colon cancer
- Aspirin use
- Alcohol intake
- Multivitamin use
- Intakes of fiber, *trans* fatty acids, saturated fatty acids, α-linolenic acid, n-6 fatty acids, glycemic load, red meat and total calories

Description of Actual Data Sample:

Initial N: 51,529 men in the original cohort

Attrition (final N): 40,230 men included in the analysis

Age: aged 40 - 75 years at baseline in 1986

Ethnicity: not reported

Other relevant demographics:

Anthropometrics

Location: United States

Summary of Results:

Key Findings

- During 18 years of follow-up, 9715 (24.1%) major chronic disease events occurred, including 3,639 cardiovascular disease events, 4,690 cancers, and 1,386 deaths from other causes (e.g. pneumonia, kidney or liver disease).
- At baseline, mean fish consumption was 0.3 ± 0.3 servings per day, and EPA + DHA consumption was 0.3 ± 0.2 g per day
- Compared with men with lower fish consumption, men with higher fish consumption were more likely to be physically active, have hypercholesterolemia and hypertension, use aspirin and multivitamin supplements, drink more alcohol, and smoke
- Men with higher fish consumption also had higher intakes of energy, protein, EPA + DHA, polyunsaturated fatty acids, fiber, fruit, and vegetables and lower intakes of saturated fat, monounsaturated fat, and *trans* fat
- In age-adjusted analyses, fish consumption was inversely associated with risk of major chronic disease (P for trend = 0.02).
- After multivariable adjustment, neither fish nor dietary n-3 fatty acid consumption was significantly associated with risk of total major chronic disease
- Compared with fish consumption of <1 serving per month, consumption of 1 serving per week and of 2 - 4 servings per week was associated with a lower risk of total cardiovascular disease of approximately 15%, but fish consumption >5 servings per week was not associated with lower risk.
- No significant associations were seen with cancer risk
- Higher or lower n-6 fatty acid intake did not significantly modify the results (P for

interaction > 0.10).

Author Conclusion:

In conclusion, consumption of fish and EPA + DHA was not associated with the overall incidence of major chronic disease in generally healthy men. Modest fish intakes (between 1 and 4 servings per week) were associated with a lower risk of total CVD. A high n-6 fatty acid intake did not modify these results.

Reviewer Comments:

Dietary intake assessed every 4 years during 18-year follow-up, but only 4 fish items were included on the food frequency questionnaire. Authors note the following limitations:

- *Study population consisted of generally healthy male health professionals, therefore the results may not be generalizable to women or to other populations*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	???

2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	No
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes

5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes

	7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes
	8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
	8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
	8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes